Ten-year analysis of transfusion in Operation Iraqi Freedom and Operation Enduring Freedom: Increased plasma and platelet use correlates with improved survival

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BACKGROUND: The Joint Theater Trauma Registry database, begun early in Operation Iraqi Freedom and Operation Enduring Freedom, created a comprehensive repository of information that facilitated research efforts and produced rapid changes in clinical care. New clinical practice guidelines were adopted throughout the last decade. The damage-control resuscitation clinical practice guideline sought to provide high-quality blood products in support of tissue perfusion and hemostasis. The goal was to reduce death from hemorrhagic shock in patients with severe traumatic bleeding. This 10-year review of the Joint Theater Trauma Registry database reports the military's experience with resuscitation and coagulopathy, evaluates the effect of increased plasma and platelet (PLT) to red blood cell ratios, and analyzes other recent changes in practice.

METHODS: Records of US active duty service members at least 18 years of age who were admitted to a military hospital from March 2003 to February 2012 were entered into a database. Those who received at least one blood product (n 3,632) were included in the analysis. Data were analyzed with respect to interactions within and between categories (demographics, admission characteristics, hospital course, and outcome). Transfusions were analyzed with respect to time, survival, and effect of increasing transfusion ratios.

RESULTS: Coagulopathy was prevalent upon presentation (33% with international normalized ratio ≥ 1.5), correlated with increased mortality (fivefold higher), and was associated with the need for massive transfusion. High transfusion ratios of fresh frozen plasma and PLT to red blood cells were correlated with higher survival but not decreased blood requirement. Survival was most correlated with PLT ratio, but high fresh frozen plasma ratio had an additive effect (PLT odds ratio, 0.22).

CONCLUSION: This 10-year evaluation supports earlier studies reporting the benefits of damage-control resuscitation strategies in military casualties requiring massive transfusion. The current analysis suggests that defects in PLT function may contribute to coagulopathy of trauma. (*J Trauma Acute Care Surg*. 2012;73: S445 S452. Copyright © 2012 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Epidemiologic study, level IV.

KEY WORDS: Transfusion ratio; coagulopathy; massive transfusion; OIF; OEF.

The Joint Theater Trauma Registry (JTTR) was established in 2004, early in the Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) conflicts, with the aim of facilitating clinical practice improvement and research.[1] The JTTR represents an unprecedented effort to create a repository of information regarding injury characteristics, clinical practices, and military trauma outcomes. Research evaluating JTTR data has produced advancements in clinical care as the OIF and OEF conflicts have progressed. Implementation of these changes was tracked through the database, outcomes were analyzed, and further refinements to clinical practice guidelines (CPGs) were used to improve care.[2] The defining approach to treatment of combat wounded that emerged from the OIF and OEF conflicts was damage-control resuscitation (DCR), a strategy focused on providing a hemostatic balance of high-quality blood products to severely injured, coagulopathic patients.[3–5]

Implementation of DCR and related CPGs entailed transfusion of component blood products in a 1:1:1 ratio of fresh frozen plasma (FFP) to platelets (PLTs) to red blood cells (RBCs) in an effort to provide a physiologically and hemostatically balanced resuscitation in approximation of shed whole blood.[3,6,7] Fresh whole blood (FWB) collected in theater when required components were unavailable or when otherwise dictated by circumstances was integrated into this strategy as a balanced, PLT-containing product, albeit one that posed greater risks of transfusion-transmitted disease. The use of the freshest available components, particularly in massive transfusion (MT) patients, was also progressively adopted to minimize potentially adverse effects of aged blood products and associated biologic

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This study was conducted under a protocol reviewed and approved by the US Army Medical Research and Materiel Command Institutional Review Board and in accordance with the approved protocol.

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changes termed the *storage lesion*.[8,10] Other important changes included the publication of the CRASH-2 trial in 2010, followed by the institution of a CPG regarding tranexamic acid (TXA) use in August 2011.[7,11]

This 10-year analysis reports the US military's experience with changing practices in resuscitation and coagulopathy as recorded in the JTTR. These data include all 3,632 US service members who received transfusions in the OIF and OEF conflicts during the first 24 hours of care.

PATIENTS AND METHODS

After regulatory approval from the Medical Research and Materiel Command Institutional Review Board was obtained, US active duty service members 18 years and older who were admitted to a military hospital in the OIF or OEF theaters of operation from March of 2003 to 2012 were entered into a database. Those who received at least one transfusion were included in the analysis. Transfusion data were only available for products received in the first 24 hours of care, without further detail as to the timing of administration. The blood products considered were RBC, FWB, FFP, or PLT units. It should be noted that only apheresis PLT units stored in plasma were transfused in theater. Each unit was recorded as a single dose in the database but was multiplied by a factor of 6 to facilitate analysis of transfusion ratios with respect to RBC units. Transfusion of cryoprecipitate could not be analyzed because one unit appeared to have been variably recorded as a unit from a single donor or a 10-pack. Given that this study was a retrospective review of deidentified data, we were unable to verify the true amount given and elected to leave potentially unreliable figures out of the analysis.

Characteristics for the entire population at time of admission were analyzed, including age, sex, Injury Severity Score (ISS), Glasgow Coma Scale (GCS) score, prothrombin time international normalized ratio (INR), systolic blood pressure, diastolic blood pressure, heart rate, temperature in degrees Fahrenheit (°F), base deficit, hemoglobin, and PLT count. Subjects were only included in the analysis of vital signs or laboratory parameters if measurable values were recorded. Data available for the first 24 hours of admission included transfusion (type and amount) and whole blood requirement (amount, if given). Analysis of medical therapy focused on the use of the hemostatic adjunct medications activated factor VII (percentage of population treated) and TXA (percentage of population treated). The Food and Drug Administration has not labeled these two drugs as they are used in theater or as discussed in this article.

Demographic data were compared between war zones (OIF versus OEF) and between survivors and nonsurvivors. The data analyzed included the number of units of RBC and/or FWB, as well as FFP and PLT transfused, age, sex, Revised Trauma Score (RTS), GCS, prothrombin time INR, ISS, time between injury and arrival to a care facility, mechanism of injury (explosive device, gunshot wound, or other), type of injury (blunt, penetrating, or burn), and service branch (Air Force, Army, Marines, or Navy).

Data were analyzed with respect to interactions within and between categories of analysis (demographics, admission characteristics, hospital course, and outcome). The transfusions (average number of RBC, FWB, FFP and PLT units per patient during the first 24 hours, as well as a combined variable of RBC added to FWB) were analyzed with respect to time during the 10-year period of review. The Joint Theater Trauma System endorsed implementation of multiple DCR CPGs, starting in 2006, which called for increased ratios of FFP and PLT to RBC transfusion; survival and transfusion data were analyzed for effects before and after these dates, as well as for the effect of increasing transfusion ratios over time. Ratios were calculated individually for FFP and PLT component therapy, respectively, by adding the number of component units to the number of FWB units (numerator) and dividing by the number of RBC added to FWB (denominator).

Survival versus mortality was compared between conflicts and with regard to time and ISS. To facilitate the interpretation of survival data between war zones, the patterns of individual body regions were reported as incidence rates calculated by dividing Abbreviated Injury Scale (AIS) scores by the total population of transfused patients in the OIF and OEF conflicts, respectively. Percentage of survival and death was then examined as a function of time for each war zone and for the total population. Because data for the full years were not available at the beginning of the period under review (2003) and the end (2012), these years were excluded for survival analysis but included in the other analyses performed.

To understand the impact of transfusion rate on mortality, the FFP and PLT ratios were divided into four categories of transfusion ratios (1, low FFP/low PLT; 2, high FFP/low PLT; 3, low FFP/high PLT; and 4, high FFP/high PLT). Low and high ratios were defined as less than or equal to 0.5 versus greater, respectively. The four ratio categories were compared with mortality and ISS, and regression analysis was used to calculate odds ratios. The effect of coagulopathy of trauma (COT), a well-recognized entity currently under intense investigation, was evaluated by comparing death and blood use between subjects with and without COT at admission, defined here as INR greater or equal to 1.5. Average INR values were compared to determine whether differences between these two groups were statistically significant. The impact of 1:1:1 resuscitation was further examined with a stepwise logistic regression model, and analyses were conducted for the entire data set, for data before and after implementation of the DCR CPG, and for the subset of MT patients (MT, defined as ≥10 of RBC + FWB in the first 24 hours of care). Although it would have been preferable to exclude from the analysis subjects who died within 1 hour of admission to minimize survival bias, this was not possible owing to a high prevalence of missing injury and/or admission times in the database. This limitation is mitigated by the longer average transport times faced by military patients. Civilian studies that eliminate those who die within the first hour generally reflect much shorter transport times and therefore represent a different patient population.

Quantitative variables with normal distribution were analyzed using the Student's *t* test; when the distribution was not normal, a nonparametric test was used (Mann-Whitney U-test). Interactions between significant effects were tested with analysis of variance (ANOVA) or stepwise multiple regression as appropriate. Simple χ^2 and Fisher's exact tests were used for qualitative variables. Tests were two-sided in all cases. Data were

TABLE 1. Demographics by War Zone: OIF and OEF

Demographic	n	OIF	n	OEF	*p*
Transfusions (RBC + FWB units), mean (SD)	2,430	10 (12)	1,202	13 (14)	<0.001
Age, mean (SD), y	2,429	26 (6)	1,199	25 (6)	0.019
Sex, male. %	2,367	97	1,191	99	<0.001
RTS, mean (SD)	1,676	6.7 ± 2.0	871	6.7 (1.9)	0.984
GCS, mean (SD)	2,235	12 (5)	1,140	12 (5)	0.893
INR, mean (SD)	1,303	1.49 (0.77)	513	1.50 (0.82)	0.773
ISS, median (IQR)	2,127	19 (13 27)	1,201	22 (14 29)	<0.001
Time to arrival, mean (SD)	1,076	54 (30)	644	54 (41)	0.735
Mechanism of injury	2,384		1,198		
Explosive device, %	1,718	72	892	74	
Gunshot wound, %	544	23	276	23	
Other, %	122	5	30	3	
Type of injury	2,367		1,193		
Blunt, %	1,191	50	177	15	
Penetrating, %	1,156	49	1,005	84	
Burn	20	<1	11	<1	
Service branch	2,430		1,202		
Air Force, %	20	<1	31	3	
Army, %	1,840	76	688	57	
Marines, %	520	21	451	38	
Navy, %	50	2	32	3	

RBC + FWB, RBC equivalent transfusion.

expressed as ±SD or SEM or as median with 25% to 75% interquartile range (IQR) as indicated. The α risk was set at 5%, and *p* value was set at <0.05.

RESULTS

Of the US active duty service members who were admitted to a military hospital from March 2003 to February 2012, 3,632 received at least one transfusion product and were included in the analysis (n = 3,632 of 26,683 patients admitted for trauma to a Role 3 military treatment facility). The population characteristics (Table 1 and Supplementary Digital Content (SDC) Table 1, http://links.lww.com/TA/A206) demonstrate that this was a severely injured population overall, with a median ISS of 20 and an IQR of 13 to 29. As a whole, patients were coagulopathic on presentation (INR, 1.5 ± 0.8) with a heart rate that was significantly elevated in this healthy, young population (106 ± 28 beats per minute). Comparative demographic data for the two conflicts (OIF and OEF, Table 1) demonstrate that time to arrival was not different, despite anecdotal reports to the contrary, and there were no differences in GCS or INR, but ISS was significantly higher for service members injured in Afghanistan. The number of OEF transfusions was higher ($p \leq 0.001$). As expected, nonsurvivors had a greater injury burden as compared with survivors; the RTS and GCS were lower, the ISS was higher, and nonsurvivors were severely coagulopathic upon arrival (INR, 2.2 ± 1.2;

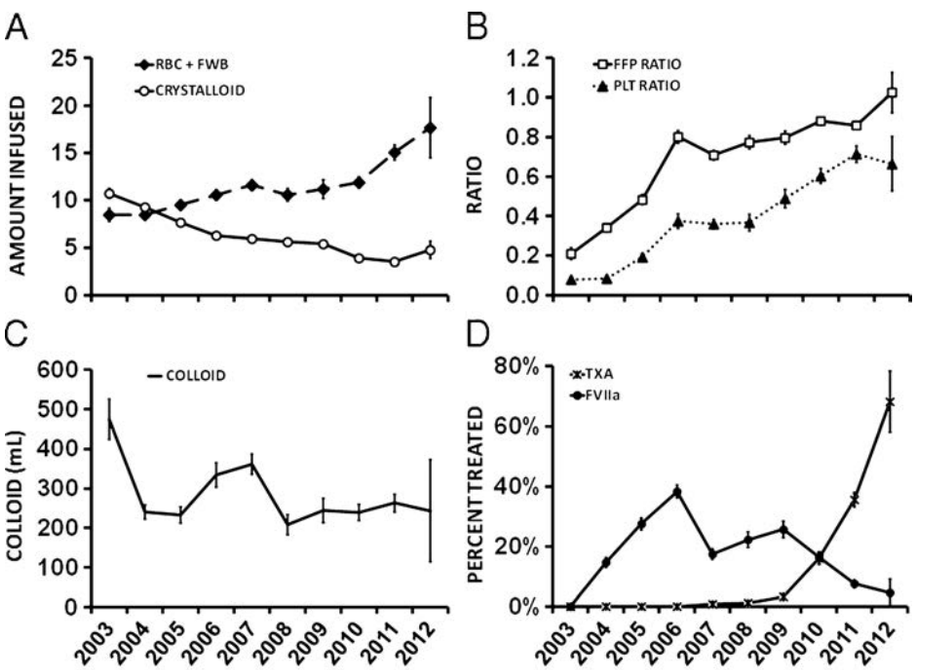

Figure 1. Analysis over time of the following: *A*, Red cell equivalent transfusion (RBC + FWB, average units; ANOVA over time $p \leq 0.001$) and crystalloid infusion (in liter, ANOVA over time $p \leq 0.001$). *B*, FFP transfusion ratio (FFP + FWB/RBC + FWB; ANOVA over time $p \leq 0.001$) and PLT ratio (PLT + FWB/RBC + FWB; ANOVA over time $p \leq 0.001$). *C*, Colloid infusion (in milliliter, ANOVA over time $p \leq 0.001$). D, Use of activated factor VII (VIIa, χ^2 for number treated over time $p \leq 0.001$) and TXA (χ^2 for number treated over time $p \leq 0.001$) as a percentage of the population treated. *Error bars* indicate SEM.

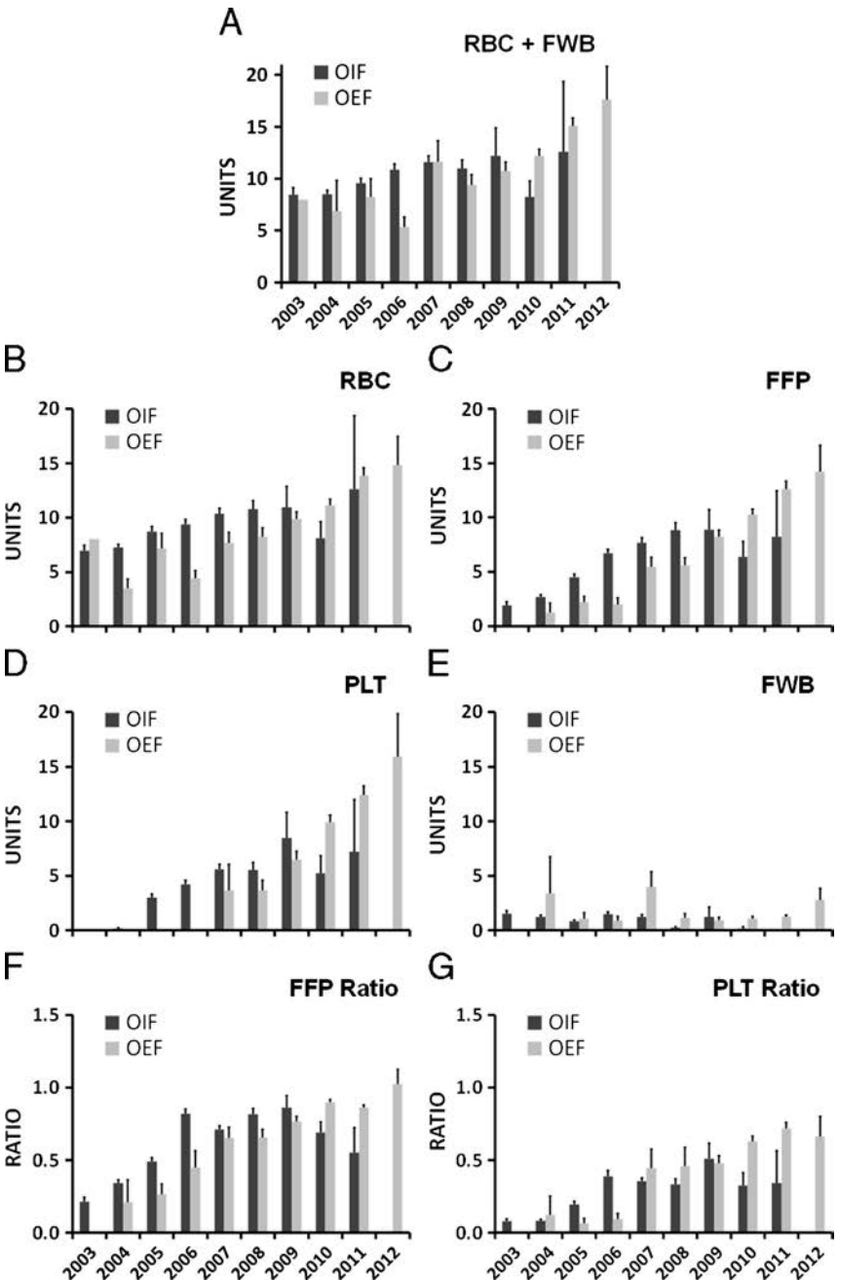

Figure 2. Transfusions by OIF (black) and OEF (light gray) conflicts over time. *A*, Red cell equivalent transfusion (RBC + FWB, average units; ANOVA over time $p \leq 0.001$; *t* test between war zones $p \leq 0.001$). *B*, Packed RBC (average units; two-way ANOVA $p < 0.05$). *C*, FFP (average units; two-way ANOVA $p < 0.05$). *D*, PLTs (average units; ANOVA over time $p \leq 0.001$; *t* test between war zones $p \leq 0.001$). *E*, FWB (average units; ANOVA over time $p \leq 0.001$; *t* test between war zones $p = 0.445$). *F*, FFP transfusion ratio (two-way ANOVA $p < 0.05$). *G*, PLT transfusion ratio (ANOVA over time $p \leq 0.001$; *t* test between war zones $p \leq 0.001$). *Error bars* indicate SEM.

$p \leq 0$ .001; SDC Table 2, http://links.lww.com/TA/A207). Survivors who did not receive an MT took approximately 10 minutes longer to arrive at a care facility; all others arrived 50 minutes after injury on average.

The total number of transfusions given increased over time (Fig. 1*A*), whereas the amount of crystalloid infused decreased ($p \leq 0.001$). The ratio of transfused components also increased steadily during the 10-year period, reflecting a move to a more hemostatic resuscitation strategy ($p \leq 0.001$, Fig. 1*B*). This practice was formalized as a CPG in 2006 that recommended RBC transfusion to be accompanied by blood components at a ratio of 1 U of RBC to a unit of FFP; the CPG was soon expanded to include PLTs and resulted in a 1:1:1 ratio. Colloid administration was more variable but generally

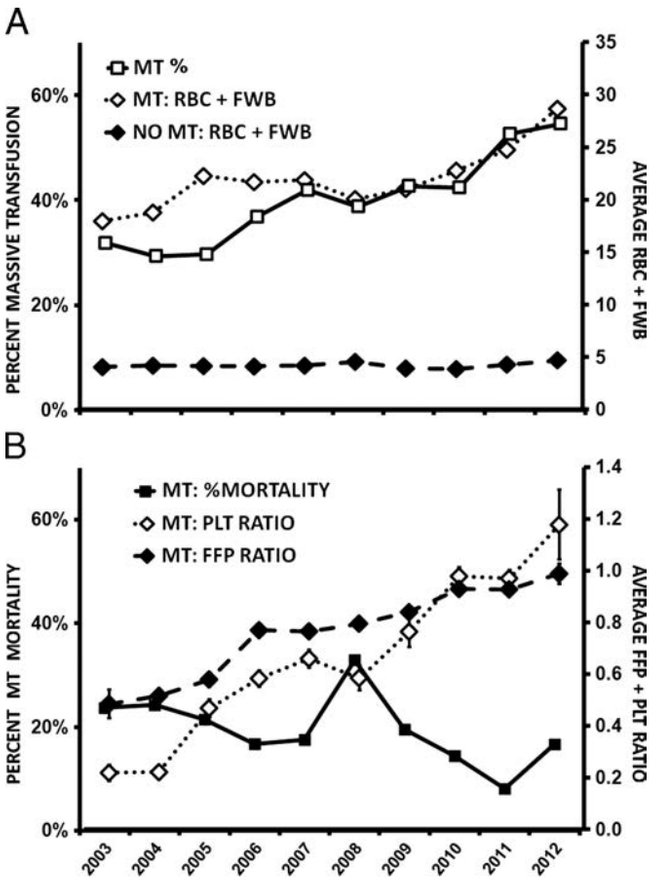

Figure 3. Transfusion requirement, transfusion ratios, and mortality in patients who met MT criteria. *A*, Percentage of patients who received MT (*open square*, left axis; ANOVA over time $p \leq 0.001$); the amount of equivalent RBCs transfused in the MT subgroup (RBC + FWB, average number of units, *open diamonds*, right axis); and the amount of equivalent RBCs transfused in the non-MT subgroup (RBC + FWB, average number of units, *closed diamonds*, right axis), two-way ANOVA $p \leq 0.001$. *B*, Mortality of MT patients (MT, %Mortality, *closed square*, left axis); MT patient PLT transfusion ratio (MT/PLT ratio, *open diamonds*, right axis); MT patient FFP transfusion ratio (MT/FFP ratio, *closed diamonds*, right axis), two-way ANOVA $p \leq 0.001$.

down-trending ($p \leq 0.001$, Fig. 1*C*). The percentage of the population treated with activated factor VII peaked in 2006 and declined to less than 10% of the population in 2012 ($p \leq 0.001$, Fig. 1*D*). Conversely, TXA was not given until 2008, initially only to US casualties treated by British forces in Afghanistan. Its use has risen steeply since the publication of the CRASH-2 trial in 2010 and the institution of a CPG regarding TXA use in August of 2011.[7,11] Approximately 70% of the transfused population received a dose in 2012 ($p \leq 0.001$, Fig. 1*D*).

Transfusions of RBC volume, plasma, and PLTs differed both between conflicts as well as over time (Fig. 2*A–E*). The amount of total RBC volume (RBC + FWB) was analyzed as a single variable and increased over time ($p \leq 0.001$, Fig. 2*A*). FFP and PLT also increased over time ($p \leq 0.001$, Fig. 2*C* and *D*). The increasing ratios of plasma and PLT units compared with RBC ($p \leq 0.001$, Fig. 2*F* and *G*) again reflect the move toward maintaining hemostasis during acute resuscitation. The average FFP-to-RBC ratio in OIF was 0.60 compared with 0.82 in OEF ($p \leq 0.001$). The average PLT-to-RBC ratio in OIF was 0.26 compared with 0.60 in OEF ($p \leq 0.001$).

Comparison of the percentage of subjects who received MT (Fig. 3) with the number of units of RBCs (RBC + FWB) given to MT versus non-MT subjects demonstrates several interesting relationships. Both the number of subjects receiving MT and the amount they received increased over time and accounted for the higher blood product use depicted in Figure 1 in the overall population. By 2011, more than 50% of subjects receiving an RBC transfusion were treated with MT, and on average, they received almost 25 U. Conversely, the average number of units given to non-MT subjects did not change over time and remained approximately 5 U throughout the 10-year period. Taken together, these data demonstrate that the military population has a high incidence of severe trauma and practice patterns changed; the amount of blood products used to resuscitate patients rose in response to increasing severity of injury over time. Interestingly, this change in severity of injury did not adversely affect survival; mortality actually decreased among MT patients. It is therefore reasonable to hypothesize that increased FFP-to-RBC and PLT-to-RBC ratios reduced mortality despite increased injury severity (Fig. 3*B*).

Questions remain regarding the military's policies on high transfusion ratios, use of FWB, and aggressive transfusion strategies. While a retrospective review cannot establish causality, we examined the associations between these policies and survival outcomes. Mortality in transfused US service members during the 10-year conflict was 16% (567 of 3,632); however, analysis of effects by year did not demonstrate a clear trend (SDC Fig. 1A, http://links.lww.com/TA/A208), even after excluding years during which a full year of data was not available (2003 and 2012). This was most likely caused by the considerable variability in overall transfused casualties from year to year. Comparing data from the OIF and OEF conflicts suggests that OEF mortality was lower (SDC Fig. 1B and C, http://links.lww.com/TA/A208), but the relationship is best clarified by comparison of the Iraq and Afghanistan survival rates to the timing of the data collected in each conflict (Fig. 4*A* and *B*). Survival and mortality characteristics from the first part of the decade under analysis are almost entirely attributable to the OIF conflict, whereas those of the later years reflect the OEF experience (Fig. 4*A* and *B*). Of note, mortality was lower in the OEF conflict, yet injury scores were higher as compared with OIF ($p \leq 0.001$, Fig. 4*C*). In addition, a greater proportion of the OEF population experienced a body area injury in every category of the AIS score ($p \leq 0.006$ for AIS 1–6, SDC Table 3, http://links.lww.com/TA/A209).

The improved survival in the OEF conflict cannot be explained by ISS, AIS, GCS, or other markers of injury severity. Grouping subjects according to whether they received low FFP/low PLT, high FFP/low PLT, low FFP/high PLT, or high FFP/high PLT demonstrates lower mortality among subjects who received the highest FFP and PLT ratios (Table 2). The most favorable odds ratio is associated with the high-FFP/high-PLT group, and lower mortality was statistically significant in that group. In

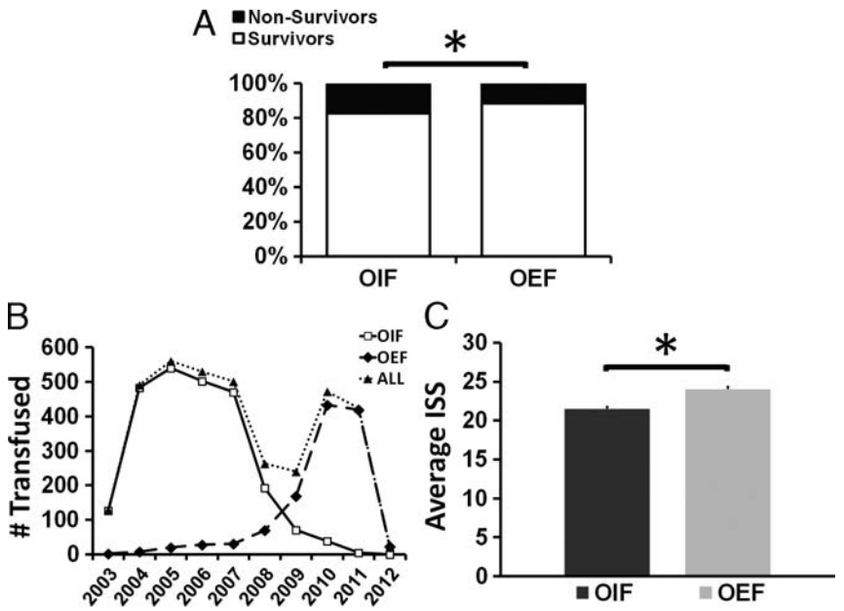

Figure 4. Comparison of OIF and OEF conflicts in terms of the following: *A*, Percentage of survivors versus nonsurvivors, $p < 0.001$. *B*, Number of subjects transfused over time in OIF (*open squares*), OEF (*closed diamonds*), and for both conflicts (all, *closed triangles*). *C*, Average ISS (OIF, black; OEF, light gray), $*p < 0.001$. *Error bars* indicate SEM.

contrast, the ISS was highest in the high-FFP/high-PLT group, demonstrating that the association with survival could not be explained by a lower injury burden. Since most of the casualties in the OEF conflict occurred later in this 10-year analysis when increased transfusion ratios were implemented and since OEF casualties received, on average, higher FFP and PLT-to-RBC ratios as reported previously, it is reasonable to hypothesize that the lower OEF mortality was driven by DCR transfusion practices.

The degree of coagulopathy at admission has a profound effect on survival (Table 3). The comparison between subjects with INR of less than 1.5 and those with INR of 1.5 or greater demonstrates that approximately a third of those with a recorded INR value at admission have a marked coagulation defect (2.2 ± 1.0; $p \leq 0.001$); this group is characterized by higher mortality and greater transfusion requirements. Given the profound injuries seen in the military population and the previously mentioned data, it is reasonable to hypothesize that by implementing aggressive transfusion practices in combination with a more hemostatic resuscitation, military trauma teams have gotten better at delivering blood and components at the critical point when they can have the greatest effect on survival.

The impact of hemostatic resuscitation was further examined with a stepwise logistic regression model. Analyses included the entire data set, the data before and after implementation of the DCR CPG, and the subset of MT patients. As suggested by the transfusion ratio groupings in Table 2, high PLT ratio in the study population (n = 2,234 for subjects meeting model criteria) had the highest association with survival with an odds ratio for mortality of 0.302 (confidence interval, 0.215–0.423, $p \leq 0.001$). FFP ratio for the entire population was significant by univariate analysis ($p \leq 0.001$), but perhaps owing to the high degree of colinearity with PLT ratio (Fig. 1*B*), the FFP variable was not significant in the regression model ($p = 0.448$). The data in Table 2 suggest, however, that high FFP ratio does have an additive effect. Other variables that were statistically significant in the model included ISS, GCS, and admission base deficit.

Analysis of the MT subgroup (n = 1,263 of 3,632 total patients or 35%) yielded similar findings for all variables with an equally strong association between PLT ratio and survival

TABLE 2. Factors Associated with Survival Outcomes: Effect of Transfusion Ratio on Survival Status

Transfusion Ratio	Low FFP, Low PLT	High FFP, Low PLT	Low FFP, High PLT	High FFP, High PLT
Odds ratio (95% confidence interval)	1.000	0.759	0.343	0.220
n	1,369	1,197	82	980
Nonsurvivors, %	17	17	16	12*
ISS	16	21†	22†	26†
IQR	10 22	14 29	14 29	18 34

*p 0.015, †$p \leq 0.001$ compared with the low-FFP/low-PLT group.

TABLE 3. Factors Associated with Survival Outcomes: Survivor Status and Blood Use Versus Coagulopathy

Parameter	INR < 1.5	INR > 1.5	p
n	1,224	592	<0.001
INR, mean (SD)	1.2 (0.2)	2.2 (1.0)	<0.001
Nonsurvivors, %	6	30	<0.001
Blood use, U per patient	6	10	<0.001
IQR	2 12	4 23	

(odds ratio, 0.124; confidence interval, 0.067–0.230; $p \leq 0.001$). High transfusion ratios in the beginning of the period of analysis were administered in a more goal-directed fashion, and it is reasonable to speculate that component transfusions arrived relatively late in resuscitation and consequently conferred less benefit. The comparison of the regression model for all patients before 2007 supports this supposition in that the association between PLT ratio and survival was not significant ($p = 0.1187$, n = 773); however, the number of subjects who met model criteria in this group was relatively low, and results should be interpreted with caution. Regression analysis for subjects treated in 2007 and after demonstrated the same findings as in the overall 10-year analysis, with a significant association between survival, PLT ratio, ISS, GCS, and admission base deficit ($p \leq 0.001$ in all cases). Once again, FFP ratio was eliminated owing to colinearity with PLT ratio. In the final regression model in which MT subjects treated before and after 2007 were compared, the number of those meeting model criteria was small (232 and 613, respectively), and yet, the association between PLT ratio and survival was strong enough to overcome the size limitations ($p = 0.008$ and ≤ 0.001).

DISCUSSION

This 10-year review of the military's experience with resuscitation and coagulopathy spans a period that saw the implementation of the JTTR database and documentation of military trauma care that has reached unprecedented levels of detail and sophistication. Access to this database has facilitated intense research efforts which, in turn, have produced rapid changes in clinical care. Nowhere is this more evident than in the speed with which the military has adopted a new DCR strategy focused on providing blood products that are both physiologically and hemostatically balanced.

Multiple CPGs have been issued since the start of the conflict, to include providing blood that is as close to FWB as possible. Storage age of blood has decreased, theoretically decreasing the storage lesion, and component therapy more closely approximates in vivo ratios. In the absence of PLTs or plasma, FWB is directly used for hemostatic resuscitation.[8]

The population characteristics for these young and healthy service members demonstrate that injury severity is high as measured by both the ISS and RTS systems. Reported average mortality for RTS of 6 to 8 is 33% to 37%, and yet, nonsurvivors were only 16% of this population, possibly indicating that CPGs have indeed improved care.[12] The prevalence of coagulopathy at admission is another indication of the high degree of injury severity in this population. Brohi et al.[13] reported that in a trauma population with a similar ISS median of 20, acute traumatic coagulopathy was present in approximately 24% and associated with a greater than fourfold mortality increase.[14] We found a similar association between coagulopathy and poor outcome in our population. Traumatic coagulopathy is associated with the confluence of tissue injury in combination with hemorrhagic shock, a prevalent finding after explosive injury, the most common mechanism of injury in our study population.[15]

The predominance of coagulopathy provides a potential rationale for previously reported associations between a high FFP transfusion ratio and beneficial outcomes among military trauma patients, in that timely and expectant, rather than so-called *goal-directed treatment*, may be needed to address acute traumatic coagulopathy.[16] Goal-directed treatment as it is practiced in theater is hampered by slow return of laboratory values, which can sometimes take more than an hour to process. Furthermore, currently available coagulation testing, which consists of prothrombin/INR and PLT count measurement, does not provide adequate information to guide therapy in the setting of complex trauma-induced coagulopathy. Abnormalities in coagulation parameters can develop within 25 minutes of injury in more than 50% of trauma patients, an important consideration for injured service members who experience mean transport times of approximately 50 minutes to an hour according to our data.[17]

While ideal transfusion ratios are a matter of debate, the importance of transfusing FFP in conjunction with RBC is widely recognized. In part owing to high ISS, severe tissue injury, and the prevalence of massive hemorrhage, a concerted effort was made during the last 5 years to meet these in-theater challenges with more aggressive MT protocols. The new CPGs produced greater amounts of blood product transfusion, higher FFP transfusion ratios, and decreased use of crystalloids. In this 10-year review, we showed that a high PLT transfusion ratio is more strongly correlated with survival than FFP ratio, as demonstrated by the comparison of low versus high transfusion ratios and by logistic regression. It is possible that colinearity between FFP and PLT ratios obscures the relative contributions of each component and that this is compounded by the fact that each unit of apheresis PLTs contains essentially one unit of plasma. In contrast, recent studies may offer clues as to possible mechanisms involved. For example, one reported that more that 45% of trauma patients had abnormal PLT aggregometry results, whereas another found that soluble CD40 ligand (sCD40L), a circulating PLT-derived mediator associated with inflammation, endothelial damage, and hyperfibrinolysis, is elevated in trauma patients.[18] sCD40L may be a key to link PLT dysfunction, potentially from early activation and PLT clearing leading to subsequent functional thrombocytopenia. Furthermore, sCD40L may reduce thrombin generation and cause hyperfibrinolysis.[18,19] Similar studies have not been conducted in a military population; however, a 2-year review at a military hospital showed improved 30-day survival for those with the highest PLT ratio.[20] In a retrospective study examining the association of blood product ratios with outcomes in patients with and without severe traumatic brain injury, increased PLT ratios were associated with improved outcomes after propensity matching and adjustment for potential confounders, whereas increased FFP ratios had increased association with survival in patients without severe traumatic brain injury.[21] How DCR concepts affect patients with and without severe traumatic brain injury needs further study. Here, we confirmed the association between high PLT ratio and better survival during a 10-year period in a data set that recorded overall survival as opposed to 30-day survival. While causality cannot be proven, the correlation may be caused by positive effects of a higher transfusion ratio, resulting in higher survival in this young and healthy population. The benefits of hemostatic resuscitation can be difficult to detect in a civilian population because outcomes are often obscured by the sequelae of extensive comorbidities and social problems. Decreased crystalloid use did

not have a significant effect on survival in our regression models, which may require further evaluation.

Recent anecdotal reports that MT rates are decreasing owing to early hemostatic resuscitation are not supported by this analysis in combat casualties. Rather, both the numbers of subjects receiving MT and the number of blood units given have increased over time. Although inappropriate transfusions cannot be ruled out as the cause in a retrospective review, a more likely explanation is that as ISS increased, coagulopathy worsened, and blood transfusion requirements followed. This interpretation of the findings is supported by the fact that mortality has decreased over time despite increases in ISS. The safety of DCR practices is often called into question; our data suggest that increased blood use with increased ratio of FFP and PLTs to RBCs in severely bleeding patients is safe and not associated with worse outcomes.

Evaluation of the demographic data was hampered by the nature of the database on which the study was based. Information was provided in a completely deidentified manner; thus, further details to elucidate data characteristics could not be provided. This was of particular relevance regarding injury types and mechanisms; categories were significantly different both between theaters and with regard to survivor status. Without a better understanding of specific injuries, these data are difficult to interpret. Similarly, statistically significant effects had to be interpreted with regard to clinically important findings because of the size of the database, which included 3,632 subjects.

Conversely, size was an advantage of the database; we were able to evaluate effects over time and within subgroups, which would not have been otherwise possible. In all, this analysis yielded important findings that will direct future basic science and clinical investigations. The strength of PLT ratio association with higher survival, despite normal admission PLT counts, warrants further investigation into the mechanisms underlying deficits seen after severe trauma and into finding ways to overcome PLT shortages inherent to austere combat environments.

A 10-year review of the US military experience with blood transfusions demonstrates that injured service members are often coagulopathic upon presentation, particularly when MT is required, and coagulopathy was associated with higher mortality. Increases in component transfusion ratios were correlated with greater survival but not decreased blood requirements. Survival was most strongly correlated with high PLT ratios, but high FFP ratios had an additive effect. PLT transfusion was associated with lower mortality in patients with normal admission PLT counts, suggesting that defects in PLT function may contribute to COT. These findings, which are consistent with results from civilian centers, support further research on how best to deliver and store PLT products in theater and on the underlying mechanisms of coagulopathy and PLT insufficiency.[22,23]

AUTHORSHIP

H.F.P., L.H.B., and A.P.C. designed this study. H.F.P., A.G.M., and A.P.L. performed data analysis; H.F.P., L.H.B., and A.P.C. interpreted the data. H.F.P., J.K.A., M.A.B., and A.P.C. performed statistical analyses. H.F.P. prepared the manuscript, which all authors critically reviewed. All authors approve of the article. H.F.P. and A.P.C. take overall responsibility for the project.

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